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The aim of this study is to characterize the relationship between major depression and the metabolic syndrome in a large community based sample of Australian men and women aged 26–90 years. A lifetime history of major depression was assessed by telephone interview following the DSM–III-R. A current history of metabolic syndrome was assessed following the United States National Cholesterol Education Program Adult Treatment Panel III (NCEP AP-III) guidelines 1 to 3 years later. Logistic regression was used to estimate the association between depression and the metabolic syndrome, and its component criteria, controlling for age, sex and alcohol dependence. There was no association between a lifetime history of major depression and the presence of the metabolic syndrome. There was a weak association between depression and low high-density lipoprotein cholesterol but not with other component criteria of the metabolic syndrome. Despite calls for interventions directed at depression to reduce the onset of the metabolic syndrome there are important failures to replicate in large samples such as this, no consensus regarding the threshold at which depression may pose a significant risk even allowing for heterogeneity across populations, and no consensus regarding confounders that may explain inter-study differences. The absence of any dosage effect of depression on the associated risk for the metabolic syndrome in other unselected samples does not support a direct causal relationship. The call for intervention studies on the basis of the currently published evidence base is unwarranted.

Keywords: depressive disorder, major; metabolic syndrome; cardiovascular diseases

The metabolic syndrome is defined by a combination of central obesity, high blood pressure, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides and hyperglycemia. These clustered risk factors have been associated with the development of type 2 diabetes and cardiovascular disease (Reaven, 1988). Identifying factors associated with the development of the metabolic syndrome is therefore of considerable public health interest. Depression may be one such factor. Depression is associated with an increased risk for diabetes and cardiovascular disease (Glassman, 2008) but the mechanisms underlying this association are still poorly understood. The metabolic syndrome may partly mediate the association. The relationship between depression and the metabolic syndrome has been examined by at least 18 studies (Table 1). A significant association has been reported for 14 samples but whether this reflects an important causal relationship or the impact of confounding or mediating variables is unclear.

A history of major depression is associated with an approximately twofold increased risk of the metabolic syndrome in community and population based samples (Goldbacher et al., 2009; Roriz-Cruz et al., 2007; Kinder et al., 2004). Depression defined by a clinically meaningful threshold applied to subject-rated symptoms is also associated with an approximately twofold increased risk of the metabolic syndrome (Skilton et al., 2007; Takeuchi et al., 2009; Vanhalla et al., 2009). Subject-rated checklists survey recent symptoms of depression and the similarity of the estimated association with the metabolic syndrome using either a lifetime history or recent symptoms of depression may indicate that the timing of depression is less important than ever meeting a clinically relevant threshold. An association between the metabolic syndrome and depression is not, however, confined to a clinically significant level of depression symptoms. Mean differences in the level and severity of subject rated depression symptoms between those with and without the metabolic syndrome are typically small and well within the normal range (Dunbar et al., 2008; Hildrum et al., 2009; Skilton et al., 2007; Takeuchi et al., 2009; Vogelzangs et al. 2007a; 2007b).

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Table 1

Previous Studies of the Association Between Depression and the Metabolic Syndrome

Author	*N*	Age range or mean (SD)	Sex	Depression measure	Association between the metabolic syndrome and depressive		Design, yrs prospective follow-up	Sample	Special features	Country
					Disorder (OR)	Symptoms (OR)				
Dunbar et al., 2008	1,345	25–84	M+F	HADS-D	✘	✔	Cross-sectional	Unselected community sample	Stratified random rural sample. OR not reported.	Australia
Gil et al., 2006	795	50 or 60 yrs	M+F	BDI	✔(M)	—	Cross-sectional	Unselected community sample	Participants offered screening for hypertension, diabetes and lipid abnormalities. OR not reported.	Poland
Goldbacher et al., 2009	429	42–52	F	SCID	**1.8**[a]	—	Longitudinal, 7	Selected community sample	Participants randomly selected within age range informative about menopausal transition. Significant longitudinal association (Dep→MetS). OR adjusted for age and race.	USA
Heiskanen et al., 2006	121	51 (9)	M+F	SCID	✔	✘	Longitudinal, 6	Selected clinical sample	All had major depression at baseline. Significant cross-sectional association at follow-up. Longitudinal association non-significant. OR not reported.	Finland
Herva et al., 2006	5,698	33	M+F	HSCL	0.9[u] 0.8[a1]	—	Cross-sectional	Unselected community sample	1966 birth cohort; A1 adjusted for gender, smoking, alcohol consumption, marital status, level of education and physical activity.	Finland
Hildrum et al., 2009	9,571	20–89	M+F	HADS-D	1.04[a1] 0.87[a2]	1.07[a1] 0.97[a2]	Cross-sectional	Unselected community sample	Population based health study. OR for symptoms is per 1 SD increase. A1 adjusted for age and gender; A2 adjusted for age, gender, education, physical activity, smoking and pulse rate	Norway
Kinder et al., 2004	6,189	17–39	M+F	DIS	**2.1**[u](F) **2.0**[a1](F) **2.0**[a2](F)	—	Cross-sectional	Population-based	Participants free of heart disease and diabetes. A1 adjusted for age and race; A2 adjusted for age, race, education, smoking, physical activity, dietary energy from carbohydrates, alcohol in past year	USA
McCaffery et al., 2003	76 MZ 73 DZ	63 (2) 62 (3)	M M	CES-D	—	✔	Cross-sectional	Selected community sample	Participants were twins and war veterans who participated in the National Heart, Lung, and Blood Institute Twin Study	USA

(continue over)

Table 1 (continued)

Previous Studies of the Association Between Depression and the Metabolic Syndrome

Author	*N*	Age range or mean (SD)	Sex	Depression Measure	Association between the metabolic syndrome and depressive		Design, yrs prospective follow-up	Sample	Special features	Country
					Disorder (OR)	Symptoms (OR)				
Pulkki-Råback et al., 2009	921	12–33	M+F	BDI	—	**1.4**[a1](F) **1.4**[a2](F) **1.4**[a3](F) **1.4**[a4](F) **1.4**[a5](F) **1.9**[a6](F) 1.4[a7](F)	Longitudinal, 21	Unselected community sample	Nationally representative sample. OR per 1 SD increase in depressive symptoms. A1 adjusted for age. A2 adjusted for childhood metabolic components; A3 adjusted for childhood SES; A4 adjusted for adult health behaviors; A5 adjusted for adult SES; A6 adjusted for C-reactive protein; A7 adjusted for all of the above. OR is for longitudinal association Dep→MetS.	Finland
Räikkönen et al., months2002	425	42–50	F	BDI	**1.3**[a1]	✔	Longitudinal, 7	Selected community sample	Participants selected if menstruated in the past 3 months and not taking HRT, diastolic BP < 100 mm Hg, not surgically menopausal, not diagnosed with diabetes or hypertension and not taking thyroid, lipid-lowering or psychotropic medications. A1 adjusted for age, menopausal status, use of hormone replacement therapy, and years of education.	USA
Räikkönen et al., 2007	432	49 (2)	F	BDI	**1.4**[u] **1.4**[a1]	✔	Longitudinal, 15	Selected community sample	As above; A1 adjusted for age, physical activity,	USA
Roriz-Cruz et al., 2007	420	60+	M+F	GDS, DSM-IV DD	**2.1**[a1] **2.0**[a2]	✔	Cross-sectional	Unselected community sample	Randomized sample of elderly residents. Participants with a history of stroke excluded from analysis. A1 adjusted for age, sex and ischaemic heart disease. A2 adjusted for A1 and components of the metabolic syndrome	Brazil
Skilton et al., 2007	1598	30–80	M+F	HADS-D	**1.6**[a1] **1.5**[a2] **1.5**[a3]	✔	Cross-sectional	Selected clinical sample	Participants ascertained from an outpatient Centre for Prevention and Detection of Atherosclerosis. Referred to Centre because of 1+ risk factor for cardiovascular disease. A1 adjusted for age, prior cardio–vascular disease, employment and marital status; A2 adjusted for A1 + smoking, dietary score and physical activity; A3 adjusted for A2 + body mass index	France

(continue over)

Table 1 (continued)

Previous Studies of the Association Between Depression and the Metabolic Syndrome

Author	*N*	Age range or mean (SD)	Sex	Depression measure	Association between the metabolic syndrome and depressive		Design, yrs prospective follow-up	Sample	Special features	Country
					Disorder (OR)	Symptoms (OR)				
Takeuchi et al., 2009	1215	20–67	M	POMS	1.4 1.9[a1]	NA	Cross-sectional	Unselected	Full-time city office workers. A1 adjusted for age, prior history community sample of cardiovascular disease, type 2 diabetes, smoking, alcohol consumption, exercise, sleep and job situation	Japan
Vaccarino et al., 2007	652	58 (11)	F	BDI	**1.8**[a1(b1)] **1.7**[a2(b2)] **1.6**[a1(b2,b3)] **1.6**[a2(b2,b3)]	NA	Longitudinal, 6	Selected clinical sample	Participants experienced chest discomfort and/or myocardial ischemia and were referred for coronary angiography. A1 adjusted for age, race, education, marital status. A2 adjusted for A1 + smoking, physical activity, functional capacity and beta-blocker use. b1 = BDI ge 10 and/or previous depression dx; b2 = BDI ge 10 or previous depression dx; b3 = subjects without a history of coronary heart disease	USA
Vanhala et al., 2009	1,294	36–56	M+F	BDI	**2.5**[a1(f)]	NA	Longitudinal, 7	Unselected community sample	All inhabitants of the Pieksämäki area in South Savo who were born in 1942, 1947, 1952, 1957 and 1962 invited for a health check up. A1 adjusted for age, education, physical activity, smoking, alcohol use, marital status, use of antidepressants and HRT. OR is for longitudinal association Dep→MetS.	Finland
Vogelzangs et al., 2007a	867	65+ 74 (7)	M+F	CES-D	**1.5**[u] 1.3[a1]	**1.3**[u] **1.2**[a1]	Cross-sectional	Unselected community sample	A prospective study of older persons randomly selected from 2 population registries. OR for symptoms represents OR per 1 SD increase in depression symptoms. A1 adjusted for age, sex, education, smoking, alcohol use, number of chronic diseases and severe renal function impairment.	Italy
Vogelzangs et al., 2007b	2917	70–79	M+F	CES-D	Na	**1.1**[u(c)] **1.1**[a1(c)]	Cross-sectional	Selected community sample	Medicare eligible, well functioning older persons. OR represents OR per 1 SD increase in symptoms. A1 adjusted for age, race, sex, education, income, smoking, alcohol use and physical activity.	USA

Note: Bold type indicates a significant association between depression and the metabolic syndrome at $p < .05$; else entries reflect a nonsignificant association; NA = not assessed; ✔ reported a significant association but not the OR; ✘ reported a nonsignificant association but not the OR; M = in Males; F = in Females; C = in Caucasians; [a] = adjusted odds ratio; [u] = unadjusted odds ratio; Dep-dx categorical definition of depression based on diagnostic interview or a validated threshold from a rating scale; Dep-sx depression symptom rating scale score; BDI Beck Depression Inventory; CES-D Centre for Epidemiological Studies Depression Scale; DIS Diagnostic Interview Schedule; DSM-IV DD minor or major depressive disorder; HADS-D Hospital Anxiety and Depression Scale Depression subscale; GDS Geriatric Depression Scale, Brazilian Portuguese validated version; HSCL Hopkins Symptom CheckList; POMS Profile of Mood States; SCID Structured Clinical Interview for DSM-IV.

Multiple episodes of depression are not associated with a greater risk for metabolic syndrome than single episodes of depression (Goldbacher et al., 2009; Kinder et al., 2004) and duration of depression does not predict future metabolic syndrome (Heiskanen et al., 2006). There is no evidence at all for a dosage effect of depression on risk for the metabolic syndrome except in clinical samples with diagnosed cardiovascular disease (Vaccarino et al., 2008) or related risk factors (Skilton et al., 2007). The population-based Norwegian HUNT study found a very weak association between depression and the metabolic syndrome was unaffected by the inclusion or exclusion of those with cardiovascular disease (Hildrum et al., 2009). An apparent dosage effect of depression on risk for the metabolic syndrome in the presence of cardiovascular risk factors in clinical samples may therefore reflect chance findings or ascertainment bias. Findings regarding the effect of temporal order on the estimated association between depression and the metabolic syndrome are inconsistent. Metabolic syndrome in adulthood did not predict the future onset of depression (Goldbacher et al., 2009; Räikkönen et al., 2002) but the metabolic syndrome in childhood predicted higher levels of depression symptoms in adulthood (Pulkki-Råback et al., 2009).

There are more reports of a positive association between depression and the metabolic syndrome in women than men (Table 1) and the possible importance of gender as a moderating variable is regularly raised. The prevalence of depression is also higher in women than men (Kessler, 2003) and there may consequently be a sex difference in power to detect an association. In the largest studies conducted to date there is no evidence that sex moderates the association between depression and the metabolic syndrome (Hildrum et al., 2009; Kinder et al., 2004).

Analysis of the individual criteria that comprise the metabolic syndrome, which may yield insights into the basis for any observed association with depression, has generated less consistent findings than analysis of the composite measure. Positive associations are most often reported between depression and central obesity/body mass index (Dunbar et al., 2008; Herva et al., 2006; McCaffery et al., 2003; Pulkki-Råback et al., 2009; Takeuchi et al., 2009; Vaccarino et al., 2007) or HDL cholesterol (Dunbar et al., 2008; Igna et al., 2008; Vanhala et al., 2009; Vogelzangs et al., 2007a) and triglycerides (Kinder et al., 2004; McCaffery et al., 2003; Pulkki-Råback et al., 2009; Vaccarino et al., 2007). Depression is therefore more often associated with the construct of metabolic syndrome than with its component parts (Vogelzangs et al., 2007b). Power to detect an association with individual criteria should be greater than power to detect an association with a (less prevalent) cluster of the same criteria unless it is the combination of the unique variance each criteria index that largely drives the association. It may be the variance indexed by the clustering of metabolic criteria that matters (e.g., elevated blood pressure *plus* abnormal HDL cholesterol *plus* elevated triglycerides rather than elevated blood pressure alone). A significant association between major depression and the metabolic syndrome is still statistically significant after adjustment for each of the individual metabolic syndrome criteria (Roriz-Cruz et al., 2007).

The aim of this report is to characterize the relationship between the clinical syndrome of major depression and the metabolic syndrome in a large community-based sample of Australian men and women aged 26 to 90 years.

Methods

Subjects

Subjects were ascertained in 1992-1993 from the volunteer Australian Twin Registry for a study of substance abuse and common psychiatric disorders. Psychiatric history was surveyed by telephone using the Semi-Structured Assessment for the Genetics of Alcoholism, adapted for the Australian population (SSAGA-Oz). A detailed account of the ascertainment of twins for this study is provided in Heath et al. (1997). Between 1993 and 1996 participants in the SSAGA-Oz study were invited to participate in a second study involving donation of a blood sample and measurement of physical characteristics. This is known as the SSAGA-Blood Study (Hansell et al., 2008; Whitfield et al., 1998). One of the main objectives of the blood study was to collect DNA and individuals were targeted for recruitment primarily if they were a dizygotic twin who had not previously donated blood (Hansell et al., 2008).

The SSAGA-Oz study comprised 5,996 individuals, 4,044 of whom were approached to participate in the SSAGA-Blood Study. Of these 3,389 (84%) participated; 3,375 provided blood samples and non-invasive physical measures, the remaining 14 provided only physical measures. The SSAGA-Blood Study comprised 2,248 women and 1,141 men and these individuals are the subject of the present report. The sample comprised 534 female–female monozygotic (MZ) pairs and 133 female MZ twins from unmatched pairs, 204 male–male MZ pairs and 93 male MZ twins from unmatched pairs, 283 female–female dizygotic (DZ) pairs and 106 female DZ twins from unmatched pairs, 110 male–male DZ pairs and 66 male DZ twins from unmatched pairs, and 282 opposite sex DZ pairs and 165 individual twins from an unmatched pair. The average age of female subjects was 45 years (range 26–90 years). The average age of male subjects was 44 years (range 30–85 years).

The SSAGA-Oz study and the SSAGA-Blood study were both approved by the institutional research and ethics committees and all subjects participating in each study gave informed consent.

Measures

The SSAGA interview was administered by telephone during 1993–1994 and included an assessment of the

subject's history of major depression. Psychiatric assessments were conducted by a team of 20 trained interviewers. All interviews were audio-taped for quality control unless the subject refused permission. Separate interviewers assessed each member of a twin pair. A lifetime history of DSM-IV major depression was assigned from the SSAGA-Oz interview data by computer algorithm (Bierut et al., 1999; Heath et al., 1997).

The metabolic syndrome was assessed in person during 1993-1996 and after the SSAGA interview. Systolic and diastolic blood pressures were measured when blood was collected using an automated blood pressure recorder (Dynamap 845 Vital Signs Monitor; Critikon Inc.) with subjects seated. The mean of two results taken at 1-min intervals was used. Body mass index was calculated from self-reported height and weight. Subjects also completed a questionnaire that included information on current and past medical conditions and listed all medications they were currently taking.

Serum was separated from blood and stored at –70°C until analysis. Total cholesterol, glucose and triglycerides were measured by Boehringer Mannheim methods on a Hitachi 747 analyzer. HDL was measured by precipitation of non-HDL with dextran/$MgSO_4$ followed by enzymatic cholesterol assay. Samples were not collected in a fasting state, but information on time of last meal/snack and type of food eaten was collected.

The United States National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III, 2001) defines the metabolic syndrome as the presence of at least three of the following five criteria:

1. Abdominal obesity: Waist circumference ≥ 102 cm for men, ≥ 88 cm for women.
2. Fasting triglycerides: ≥ 150 mg/dL (1.7 mmol/L) or relevant drug treatment.
3. HDL: < 40 mg/dL (0.9 mmol/L) for men, < 50 mg/dL (1.1 mmol/L) for women.
4. Blood pressure: systolic blood pressure ≥ 130 mmHg and/or diastolic ≥ 85 mmHg or antihypertensive medication.
5. Fasting glucose: ≥ 100 mg/dL (5.6 mmol/L) or insulin/hypoglycemic medication.

The SSAGA-Blood study did not measure waist circumference but did measure body mass index (BMI). Waist circumference and BMI are highly correlated (Bigaard et al., 2003) and obesity (BMI > 30kg/m^2) was therefore used to define NCEP ATP-III criterion 1 rather than abdominal obesity.

Assays for plasma triglycerides and glucose are affected by recent food ingestion and medication can correct elevated blood pressure, glucose or lipids. The guidelines of Meyer et al. (2008) are therefore used for non-fasting samples and for subject's using relevant medication:

1. The NCEP ATP-III glucose criterion is considered met if subjects were (a) on prescribed hypoglycemic medications (b) using insulin or (c) had random glucose greater than or equal to 200 mg/dL (11.1 mmol/L).
2. The NCEP ATP-III glucose criterion is considered *not met* if the non-fasting measure is less than 100 mg/dL (5.6 mmol/L).
3. A nonfasting glucose between 100–199 mg/dL (5.6–11 mmol/L) is treated as missing.
4. The NCEP ATP-III triglyceride criterion is considered *not met* if the random serum value is less than 150 mg/dL (1.7 mmol/L).
5. A nonfasting triglyceride value of 150 mg/dL (1.7 mmol/L) or more is treated as missing.
6. The NCEP ATP-III blood pressure criterion is considered met if the value is above the cut-off *or* the subject is taking anti-hypertensive medication.
7. The NCEP ATP-III HDL cholesterol criterion is considered met if the value is below the cut-off.
8. The triglyceride criterion is considered met if the subject is taking relevant medication.

Subjects were deemed to be taking relevant medication if they recorded the name of the relevant medication they were using on the survey questionnaire. Those who reported having diabetes were considered to have met the criterion for elevated glucose.

Information on time between sample collection and last meal was available for 3,049 participants. The mean number of hours between food intake and sample collection was 3.9, with a range of less than 1 hour to 24 hours. The time elapsed between last meal and sample collection was eight hours or greater for 412 (14%) of participants.

Subjects met criteria for the metabolic syndrome if they met any three of the modified NCEP ATP-III criteria.

Statistical Methods

Logistic regression is used to evaluate participation bias. The dependent variable is participation in the SSAGA-OZ Blood study by participants in the larger SSAGA-Oz study. Logistic regression is used to evaluate bias associated with missing data. The dependent variable is missing data for the estimation of the metabolic syndrome amongst participants in the SSAGA-Blood study. The representativeness of the SSAGA-Blood study sample is estimated by conducting a comparison with the AusDiab study (Cameron et al., 2008). AusDiab ascertained a representative sample of 11,247 non-institutionalized Australians over the age of 24. Multiple logistic regression is used to test if a lifetime history of major depression is associated with the presence of the metabolic syndrome, adjusting for the subject's age, sex, and level of alcohol dependence which was a focus of the original SSAGA-Oz study. The dependent variable is the metabolic syndrome. In the absence of an observed association between major depression and the metabolic syndrome within individuals, a conditional logistic

regression will be used to confirm the absence of an association within twin pairs because negative confounding due to familial effects could mask a within family association. There were n = 224 twin pairs discordant for a lifetime history of major depression who had non-missing metabolic data. Means and associated 95% confidence intervals are estimated for continuous outcome measures and covariates. Proportions are estimated for categorical variables. Odds ratios are used to summarize the estimated association between lifetime history of major depression and the presence of the metabolic syndrome, and between lifetime history of major depression and each of the component criteria of metabolic syndrome. Data from twin pairs is not statistically independent. Standard errors are therefore calculated using robust estimators of variance (Williams, 2000). These analyses were conducted using Stata 10.1 for Macintosh (Stata Corporation, 2008).

Results

Participation Bias

Participation in the SSAGA-OZ Blood study is not predicted by age (p = 0.67) or history of major depression (p = 0.31) or alcohol dependence (p = 0.79). Males were less likely to participate than females (O.R. = 0.80, 95% C.I. = 0.65 – 1.00, p = 0.05). Age (p = 0.56), history of major depression (p = 0.99) or alcohol dependence (p = 0.97) and gender (p = 0.09) do not differ significantly between participants in the SSAGA-OZ Blood Study and the full SSAGA-OZ sample.

Bias Associated With the Pattern of Missing Data

The criteria for the metabolic syndrome could be estimated for 2,525 participants (75%) of the SSAGA-OZ Blood study. Complete metabolic data was not obtained for all individuals (Table 2) and some data are not missing at random. Women are less likely to have missing data for blood pressure (O.R. = 0.79, 95% C.I. = 0.66–0.94, p < .01) or serum glucose than men (O.R. = 0.75, 95% C.I. = 0.62–0.92, p < .01). Women are more likely to be missing HDL cholesterol data then men (O.R. = 1.57, 95% C.I. = 1.10–2.26, cholesterol p = .01). Gender did not predict missing height or weight. Age did not predict missing data for any variable. Neither major depression nor alcohol dependence predicted any missing metabolic data.

Comparability With a Nationally Representative Sample

The prevalence of the metabolic syndrome was lower in SSAGA-OZ Blood study (6%) than in the AusDiab study (15–30% depending upon definition used; Table 3). In all other respects participants in the

Table 2

Prevalence of a Lifetime History of Major Depression and the Metabolic Syndrome

Measure	Female		Male		Total	
	%	No.	%	No.	%	No.
Lifetime history of major depression						
No	77.4	1740	84.2	961	79.7	2701
Yes	22.6	508	15.8	180	20.3	688
Missing		0		0		0
Metabolic syndrome						
No	94.3	1638	94.2	742	94.3	2380
Yes	5.7	99	5.8	46	5.7	145
Missing		511		353		864
Obese						
No	84.8	1879	88.5	993	86.1	2872
Yes	15.2	336	11.5	129	13.9	465
Missing		33		19		52
High blood pressure						
No	55.7	648	39.4	258	49.8	906
Yes	44.3	515	60.6	397	50.2	912
Missing		1085		486		1571
Low HDL cholesterol						
No	88.2	1896	87.8	932	88.1	2828
Yes	11.8	254	12.2	129	11.9	383
Missing		98		80		178
High triglycerides						
No	95.0	1503	86.3	503	92.7	2006
Yes	5.0	79	13.7	80	7.3	159
Missing		666		558		1224
Elevated glucose						
No	65.2	1271	70.0	671	66.8	1942
Yes	34.8	679	30.0	287	33.2	966
Missing		298		183		481

Table 3

Comparability of the SSAGA-OZ Blood Study Sample With the Nationally Representative AusDiab Sample

Measure	SSAGA-OZ Blood study mean	AusDiab mean
Age (years)		
Female	45.5	50.6
Male	43.9	51.3
Total	44.9	50.9
BMI (kg/m^2)		
Female	25.0	26.4
Male	25.7	27.0
Total	25.2	26.7
Systolic blood pressure (mmHg)		
Female	125.0	124.8
Male	131.6	131.5
Total	127.4	127.8
Diastolic blood pressure (mmHg)		
Female	75.6	66.2
Male	80.8	74.6
Total	77.5	70.0
Serum HDL cholesterol (mmol/L)		
Female	1.6	1.6
Male	1.2	1.3
Total	1.4	1.4
Serum triglycerides (mmol/L)*		
Female	1.5	1.1
Male	2.2	1.4
Total	1.8	1.3
Plasma glucose (mmol/L)*		
Female	5.1	5.2
Male	5.3	5.5
Total	5.2	5.4

SSAGA-OZ Blood study are broadly comparable to those in the AusDiab study.

Relationship Between the Metabolic Syndrome and Depression

There are no significant differences in the metabolic outcomes of individuals with or without a history of major depression (Table 4). The association between a lifetime history of major depression and the metabolic syndrome is not significant (Table 5). There is no main effect of gender on risk for the metabolic syndrome (p = .59) in a multiple regression model controlling for history of major depression (p = .45) but risk did increase with age (OR = 1.04 for age coded in years, 95% CI = 1.03–1.05, p < .001). There is a weak association between low HDL and a history of major depression (Table 5). The associations between all other individual criteria for the metabolic syndrome and a history of depression are small and nonsignificant (Table 5).

A conditional logistic regression confirmed the absence of an association between depression and the metabolic syndrome within twin pairs, adjusting for sex and zygosity. Considering only MZ pairs discordant for a history of major depression where the dependent variable was the metabolic syndrome and the independent variable was major depression (sex was not included as MZ twins are always the same sex), the association between the metabolic syndrome and depression was nonsignificant (OR = 1.33, 95%CI = 0.46–3.84, P = .59). Considering only DZ pairs discordant for a history of major depression where the dependent variable was the metabolic syndrome and the independent variables were major depression and sex, the association between the metabolic syndrome and depression was also non-significant (OR = 1.17, 95%CI = 0.36–3.47, P =.78). The association with sex was nonsignificant (p = .99). Combining MZ and DZ twins in a single model, the interaction between zygosity and major depression, and zygosity and major depression and sex, and the main effect of sex were all non-significant in association with the metabolic syndrome. A reduced model including only major depression as the dependent variable indicated no significant association between depression and the metabolic syndrome in this subsample of discordant twins (OR = 0.94, 95%CI = 0.46–1.9, P = .86). There is therefore no evidence of negative confounding due to familial effects, and consequently no evidence of an association between major depression and the metabolic syndrome in this community sample.

Discussion

This is the first Australian study to examine the relationship between major depressive disorder and risk for the metabolic syndrome, and in this sample there was no association. This study ascertained a large

Table 4

Characteristics of Subjects With and Without a Lifetime History of Depression

	Lifetime history of depression		No history of depression	
	Mean	Range	Mean	Range
Body mass index (kg/m^2)	25.3	13–44	25.2	15–49
Systolic blood pressure (mmHg)	126.2	92–186	127.7	86–109
Diastolic blood pressure (mmHg)	77.2	51–119	77.6	44–119
Serum HDL cholesterol (mmol/L)	1.4	0.6–3.0	1.4	0.6–3.5
Serum triglycerides (mmol/L)	1.8	0.4–9.2	1.7	0.3–19.3
Plasma glucose (mmol/L)	5.2	2.9–14.1	5.2	2.4–21.8
Metabolic syndrome	6%	—	6%	—

community based sample of men and women that covered the entire adult age range, administered a clinical interview to assess lifetime history of major depression and assessed that lifetime history 1–3 years before the assessment of the metabolic syndrome following international guidelines. One previous Australian study reported a significant difference in the mean level of subject-rated depression symptoms among individuals with and without the metabolic syndrome but in both groups mean depression scores were well within the normal range (Dunbar et al., 2008). When a clinically meaningful threshold was used to define possible cases of depression the association between depression and the metabolic syndrome in that study was nonsignificant, consistent with our own findings.

The study conducted by Dunbar and colleagues is worth scrutinizing because like many other studies they report significant but small group differences and they surveyed a stratified random sample that is unlikely to be biased. The 7-item HADS depression subscale used to assess recent symptoms of depression rates each symptom on a scale from 0-3 and the total depression score may therefore range between 0 and 21, with higher scores reflecting higher levels of depression. The normal range is defined as a score < 8. The mean symptom rating among individuals with and without the metabolic syndrome was 3.4 and 2.9 respectively. Individuals with and without the metabolic syndrome therefore had depression scores that were well within the normal range. Another study that used the HADS depression subscale ascertained a sample referred by a primary care physician to an outpatient Centre for Prevention and Detection of Atherosclerosis because of the presence of at least one traditional cardiovascular risk factor (Skilton et al., 2007). The mean HADS depression symptom rating in those with and without the metabolic syndrome in that study was 5.3 versus 4.4 in men and 6.5 versus 5.3 in women. Subjects *without* the metabolic syndrome in a non-random sample enriched for cardiovascular risk factors therefore had a higher mean HADS depression score than subjects *with* the metabolic syndrome in a random stratified population based sample. A HADS depression score alone clearly cannot be used to determine who is at risk of developing the metabolic syndrome, and very small mean differences that are well within the normal range should not be over interpreted. In the only other study we located that used the HADS depression subscale the weak association between depression and the metabolic syndrome was entirely confounded (Hildrum et al., 2009).

Several studies have reported an association between the metabolic syndrome and low levels of depression but not with common covariates of depression such as anxiety (e.g., Hildrum et al., 2009; Skilton et al., 2007; Takeuchi et al., 2009; Vogelzangs et al., 2007b). This apparent specificity may point away from an important comorbidity with major depression and towards something only modestly correlated with it. If covariates explain the association between depression and the metabolic syndrome then variation in the presence or prevalence of these covariates may account for inter-study differences. In the largest population based study conducted to date the authors reported a very weak association between depression and the metabolic syndrome that was entirely confounded, mainly by physical activity and education (Hildrum et al., 2009). It is therefore important to identify which factors reliably account for an association between depression and the metabolic syndrome because these factors may play an important role in linking behavioral and physical health outcomes, and, if evidence for a causality is demonstrated, they may be a better target for intervention directed at the metabolic syndrome than depression (cf. Dunbar et al., 2008; Goldbacher et al., 2009).

There may be heterogeneity within the metabolic syndrome and associated variation in outcome (Kahn, 2007). The syndrome requires at least three criteria to be present but studies do not typically report the pattern of criteria observed within their samples and many studies, including our own, use slightly modified criteria. Investigating associations with individual criteria of the syndrome only partly addresses the issue if it is the clustering of risk factors that is important. We did, however, find a weak association between low HDL cholesterol and a history of major depression,

Table 5

Association Between a Lifetime History of Major Depression and the Metabolic Syndrome

	Metabolic syndrome OR (95%CI)	Blood pressure OR (95%CI)	HDL cholesterol OR (95%CI)	Trigylcerides OR (95%CI)	Glucose OR (95%CI)	Obesity OR (95%CI)
Total						
Unadjusted	1.10 (0.74–1.65)	0.99 (0.78–1.24)	1.33 (1.04–1.72)	1.05 (0.69–1.59)	1.09 (0.89–1.32)	1.17 (0.92–1.5)
Adjusted	1.21 (0.76–1.89)	1.17 (0.87–1.55)	1.58 (1.19–2.10)	1.21 (0.78–1.87)	1.10 (0.89–1.36)	1.13 (0.88–1.44)
Females						
Unadjusted	1.11 (0.70–1.75)	1.02 (0.84–1.35)	1.31 (0.97–1.76)	1.10 (0.62–1.92)	1.10 (0.88–1.38)	1.1 (0.83–1.45)
Adjusted	1.19 (0.71–2.02)	1.20 (0.84–1.71)	1.56 (1.11–2.20)	1.17 (0.64–2.13)	1.13 (0.88–1.45)	1.08 (0.82–1.43)
Males						
Unadjusted	1.10 (0.48–2.52)	1.13 (0.72–1.76)	1.42 (0.88–2.26)	1.33 (0.71–2.52)	0.97 (0.66–1.44)	1.27 (0.76–2.14)
Adjusted	1.24 (0.53–2.93)	1.15 (0.72–1.84)	1.71 (1.03–2.82)	1.18 (0.62–2.25)	1.03 (0.69–1.55)	1.28 (0.76–2.15)

consistent with some (e.g., Dunbar et al., 2008; Maes et al., 1997; Vanhala et al., 2009;) but not all (Brunner et al., 2002) previous studies.

Understanding the relationship between depression and risk for the metabolic syndrome is important because a history of depression predicts future risk for heart disease. Variables reported to mediate the observed association between depression and the metabolic syndrome include socio-economic and lifestyle variables but these do not explain the observed association in all samples. There may be both direct and indirect pathways between depression and the metabolic syndrome (Igna et al., 2008); HDL, indices of socio-economic status and lifestyle factors may all be important.

Despite calls for interventions directed at depression to reduce the onset of the metabolic syndrome there are important failures to replicate in large samples, no consensus regarding the threshold at which depression may pose a significant risk and, currently, no consensus regarding confounders that explain inter-study differences. The absence of any dosage effect of depression on the associated risk for the metabolic syndrome in other unselected samples does not support a direct causal relationship. The call for intervention studies on the basis of the currently published evidence base is unwarranted.

Limitations

There are several limitations of the current study that should be considered when interpreting the findings presented here. First, the assessment of a lifetime history of major depression was always conducted before the assessment of the metabolic syndrome but the time between assessments was no more than 3 years. In some cases, therefore, the time between an episode of major depression and the assessment of the metabolic syndrome was less than three years. Second, the criteria used to define the metabolic syndrome vary slightly from those recommended by the NCEP ATP-III (2001). Third, participants in this study had a lower prevalence of the metabolic syndrome than the wider Australian community (Cameron et al., 2008), consistent with a bias towards participation by physically healthier subjects. The prevalence of a lifetime history of major depression in this sample is, however, consistent with estimates from other community-based samples, at around 20%, and if there had been an important association with the metabolic syndrome we should have observed it in this sample.

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